



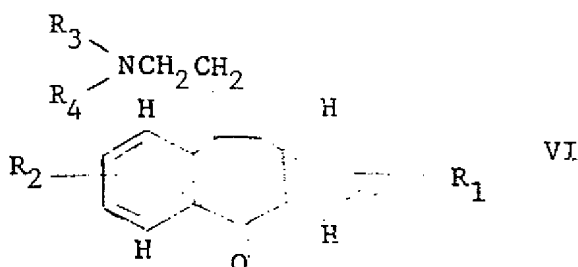
(11) AU-B1-18586/76

(12) PATENT SPECIFICATION  
ABRIDGEMENT  
(19) AU

- (21) 18586/76 503,490 (22) 12.10.76  
(23) 12.10.76 (24) 7.2.72  
(43) 23.12.76 (44) 6.9.79  
(51)<sup>2</sup> C07C 97/10 C07C 101/42.  
(54) AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE DERIVATIVES.  
(62) 51834/72.  
(71) SANDOZ PATENTS LIMITED.  
(72) HOULIHAN, W.J., NADELSON, J.  
(74) DM  
(56) 55766/73 485383 09.66-1 09.65-4 87.19 09.62-20  
09.61-2  
51834/73 477574 09.66-1 09.65-4 87.19 09.61-2  
09.66-7 09.66-991

(57) Compounds of formula VI as defined in claim 1 are also claimed.

CLAIM 1. A process for the production of a compound of formula VI,



in which R<sub>1</sub> signifies hydrogen, alkyl or alkoxy of 1 to 3 carbon atoms or fluorine,

R<sub>2</sub> signifies hydrogen, alkyl or alkoxy of 1 to 3 carbon atoms, fluorine or trifluoromethyl, and

R<sub>3</sub> and R<sub>4</sub> independently signify alkyl of 1 to 3 carbon atoms,

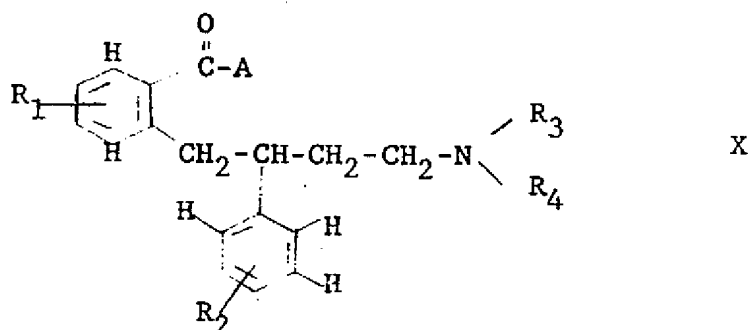
comprising cyclising, in the presence of a Lewis acid, a compound of formula X,

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in which  $R_1$  to  $R_4$  are as defined above, and

A signifies hydroxyl, straight chain alkoxy of 1 to 4 carbon atoms or chlorine.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

APPLICATION FOR A PATENT

18,586 /76 **503,490**

~~±~~  
We SANDOZ PATENTS LIMITED, 789 Don Mills Road,  
Don Mills, Prov. Ontario, Canada

hereby apply for the grant of a Patent for an invention entitled:

"AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE DERIVATIVES"

which is described in the accompanying ~~provisional~~ <sup>complete</sup> specification.  
This application is a separate application made by virtue of sub-  
section (1) of Section 49A of the Patents Act 1952 in respect of  
an invention disclosed in the complete specification lodged in  
respect of Australian Application No. 51834/73.  
~~The application is a convention application and is based~~  
on the application(s) for patent or similar protection made

in

on

in

on

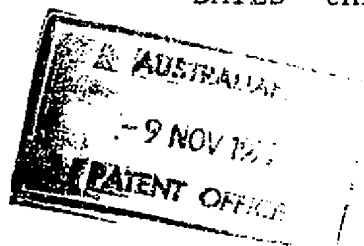
under No.

under No.

APPLICATION ACCEPTED AND AMENDED  
11/7/77  
ALLOWED

~~My~~  
Our address for service is care of DAVIES & COLLISON,  
Patent Attorneys, of 1 Little Collins Street, Melbourne, in  
the State of Victoria, Commonwealth of Australia.

DATED this 8 day of November 1977



*H. d. Rimington*

(a member of the firm of DAVIES & COLLISON)  
for and on behalf of the applicant

TO: The Commissioner of Patents  
WODEN ACT 2606

## COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1982-1989

DECLARATION IN SUPPORT OF CONVENTION OR  
NON-CONVENTION APPLICATION FOR A  
18,586 /76 PATENT OR PATENT OF ADDITION

(The declaration shall be made by the applicant: or, if the applicant is a body corporate, by a person authorized by the body corporate to make the declaration on its behalf).

In support of the Application made for a ~~patent~~  
~~patent of addition~~ for an invention entitled

Insert title of invention.

"AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE  
DERIVATIVES"

Insert full name(s) and address(es)  
of declarant(s).

✠  
We, Jean Kramer and Hans Rudolf Haus, both  
of Sandoz Patents Limited a Canadian Body Corporate  
of 789 Don Mills Road, Don Mills, Prov., Ontario  
Canada,

do solemnly and sincerely declare as follows:-

1. (a) ~~I am~~ the applicant..... for the ~~patent~~  
~~We are~~ authorized by ~~patent of addition~~  
or (b) ~~I am authorized by~~

SANDOZ PATENTS LIMITED

the applicant..... for the ~~patent~~  
~~patent of addition~~ to make this declaration on ~~its~~  
~~their~~ behalf.

2. (a) ~~I am~~ the actual inventor..... of the invention  
~~We are~~

or (b) William J. Houlihan, 15 Raynold Road, Mountain  
Lakes, New Jersey, United States of America, Jeffrey  
Nadelson, 194 Elmwood Road, Lake Parsippany, New Jersey,  
United States of America

~~is~~  
~~are~~ the actual inventor(s)..... of the invention and the facts upon which the applicant.....  
~~is~~  
~~are~~ entitled to make the application are as follows:-

The inventors have assigned the invention to  
the said applicant

(Paragraphs 3 and 4 apply only to Convention applications).

3. The basic application..... as defined by Section 141 of the Act ~~was~~  
~~were~~ made  
in..... on the.....  
by.....  
in..... on the.....  
by.....

Insert country and date of filing  
of ~~the~~ application on which priority  
is based.

Insert full name of applicant in  
each basic application.

15 NOV 1976  
PATENT OFFICE

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~  
~~were~~ the first application..... made in a Convention country in respect of the invention the subject  
of the application.

Signature(s) of declarant(s).

Declared at BASLE this 20 day of October 1976.

(No attestation or other signature  
is required).

Note: Initial all Alterations.

SANDOZ Patents Limited

*[Signature]*

## COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1969

## COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE :

**503,490**

Class

Int. Class

Application Number :

Lodged :

Complete Specification Lodged

Accepted

Published

Priority :

Related Art

**18,586 /76**I hereby declare that the  
above specification is under  
Section 17

and is correct for printing.

**22 AUG 1979**

Name of Applicant : SANDOZ PATENTS LIMITED

Address of Applicant : 789 Don Mills Road, Don Mills  
Ontario, CanadaActual Inventor(s) : WILLIAM J. HOULIHAN  
JEFFREY NADELSONAddress for Service : DAVIES & COLLISON, Patent Attorneys,  
Little Collins, Cromwell Building, 374 Bourke Street, Melbourne, 3000

AUSTRALIAN

12 OCT 1976

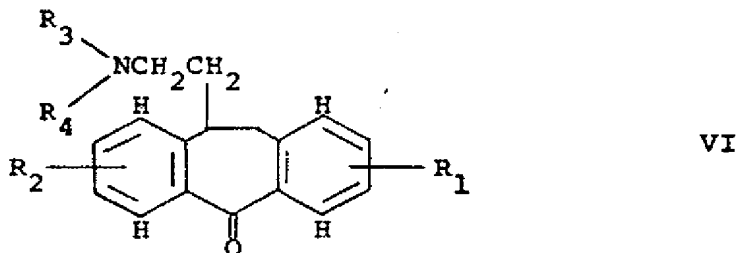
PATENT OFFICE

Complete Specification for the invention entitled :

**"AMINOALKYL-DIBENZOCYCLOHEPTEN-5-ONE DERIVATIVES"**The following statement is a full description of this invention, including the best method of performing  
it known to :-

This invention relates to aminoalkyl-dibenzo-cyclohepten-5-one derivatives.

More particularly, this invention provides  
5 compounds of formula VI,

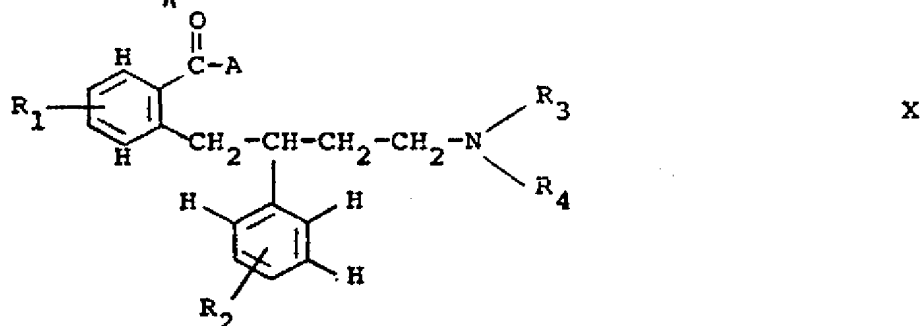


in which  $R_1$  signifies hydrogen, alkyl or  
alkoxy of 1 to 3 carbon atoms or  
fluorine,

$R_2$  signifies hydrogen, alkyl or  
alkoxy of 1 to 3 carbon atoms,  
fluorine or trifluoromethyl, and

$R_3$  and  $R_4$  independently signify  
alkyl of 1 to 3 carbon atoms.

The invention also provides a process for the  
15 production of a compound of formula VI, which comprises  
in the presence of a Lewis acid,  
cyclising a compound of formula X,



in which  $R_1$  to  $R_4$  are as defined above, and

A signifies hydroxy, straight chain alkoxy  
of 1 to 4 carbon atoms or chlorine.

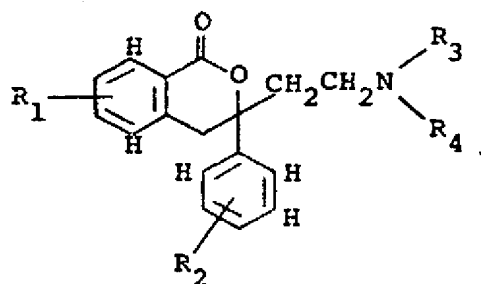
When A signifies hydroxyl or alkoxy, the cyclisation is preferably effected using a strong Lewis acid such as stannic tetrachloride, ferric chloride or titanium tetrachloride. It is preferred to carry out the reaction in the presence of an inert organic solvent such as dichloromethane, carbon tetrachloride, carbon disulphide or nitrobenzene. When A signifies chlorine, the reaction is effected using a strong Lewis acid, preferably in the presence of a solvent, as mentioned above. Suitable reaction conditions generally are from 20 to 150°C, preferably from 100 to 120°C. Reaction times are generally about 2 to 10 hours, and under preferred conditions are about 3 to 5 hours.

Compounds of formula X in which A signifies hydroxyl may be prepared by reducing a compound of formula XI,

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XI

in which  $R_1$  to  $R_4$  are as defined above.

Reduction methods particularly suitable are hydrogenation in the presence of a noble metal catalyst in the presence of an inert solvent and reduction by a zinc-ammonium hydroxide system. In the hydrogenation reaction, suitable catalysts are palladium, platinum and rhodium, and these may be neat or on a support such as charcoal. Suitable solvents are alkanols of 1 to 4 carbon atoms, such as ethanol, or acetic acid. Hydrogen pressures are conveniently about 35 to 100 psi, preferably 50 to 55 psi, and reaction temperatures are conveniently from 20 to 80°C, preferably 25 to 35°C. It is preferred to carry out the reaction in the presence of a catalytic amount of an aqueous mineral acid such as hydrochloric, sulphuric or perchloric acid. It is preferred to stop the reaction after absorption of one equivalent of hydrogen. The reduction using zinc-ammonium hydroxide is suitably carried out in the presence of a

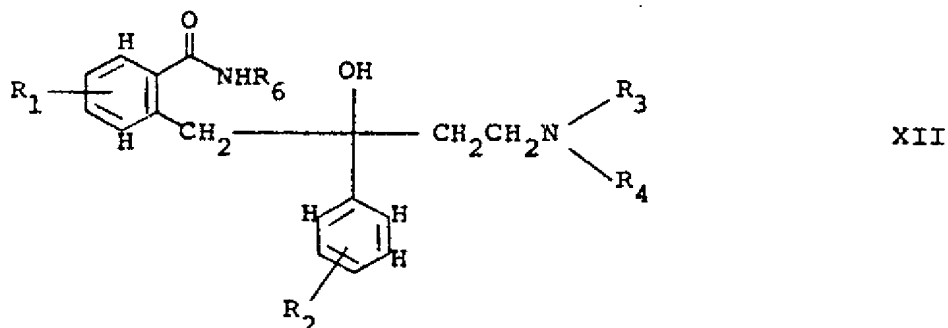
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catalyst such as cupric sulphate, and is preferably carried out in the presence of an inert organic solvent such as a lower alkanol, e.g. methanol or, especially, ethanol. Suitable reaction temperatures are from 60 to 100°C, preferably 75 to 85°C. Reaction times are generally from about 24 to 48 hours, under preferred conditions 28 to 30 hours.

The compounds of formula X in which A signifies chlorine or alkoxy may be prepared from the acids in conventional manner.

The compounds of formula XI may be prepared by cyclising a compound of formula XII,

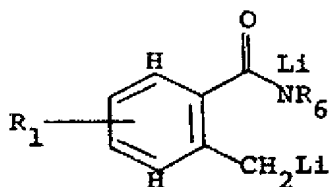


in which  $R_1$  to  $R_4$  are as defined above, and  $R_6$  signifies alkyl of 1 to 4 carbon atoms.

The cyclization is preferably effected by heating the compound of formula XII, conveniently at about 60 to 220°C, preferably at 140 to 160°C, for

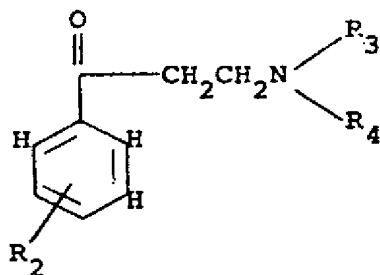
about 15 to 48 hours, under preferred conditions 20 to 28 hours. The compound of formula XII may be heated in an inert organic solvent such as tetrahydrofuran, or a hydrocarbon or halogenated hydrocarbon such as hexane, heptane, benzene, toluene or o-dichlorobenzene. It is preferred to heat the compound of formula XII under an inert atmosphere, e.g. under nitrogen.

The compounds of formula XII may be prepared by reacting a compound of formula XIII,



XIII

in which  $R_1$  and  $R_6$  are as defined above, with a compound of formula XIV,



XIV

in which  $R_2$ ,  $R_3$  and  $R_4$  are as defined above,  
in an inert organic solvent and under an inert atmosphere,  
followed by hydrolysis of the reaction product in  
conventional manner.

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Suitable solvents include diethyl ether,  
tetrahydrofuran, hexane, heptane, benzene and mixtures  
thereof. The reaction is conveniently effected under  
nitrogen, suitably at a temperature from  $-30$  to  $-15^{\circ}\text{C}$ ,  
preferably  $-25$  to  $-20^{\circ}\text{C}$ . Reaction times are generally  
about 1 to 3 hours. The compound of formula XIV is  
preferably added in solution in the inert organic  
solvent to a cold ( $-30$  to  $-15^{\circ}\text{C}$ ) inert organic solvent  
solution of the compound of formula XIII. The hydrolysis  
is preferably effected with aqueous ammonium chloride  
solution in conventional manner, preferably at a temp-  
erature of from  $-15$  to  $-5^{\circ}\text{C}$ .

The compounds of formula X exist in acid  
addition salt form and may be prepared from the  
corresponding free bases and vice versa in conventional  
manner, and may be used in salt form in the reaction  
described hereinbefore.

The compounds of formulae X, XI and XII may be  
isolated and purified using conventional techniques  
such as crystallisation, evaporation or filtration.

Certain of the compounds of formulae XIII and XIV are known and may be prepared by methods described in the literature, and those compounds whose preparation is not specifically described may be prepared by known methods or methods analogous to known methods from known starting materials.

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A preferred group of the compounds of formula VI is that in which  $R_1$  and  $R_2$ , which may be the same or different, each signifies hydrogen or fluorine, and  $R_3$  and  $R_4$ , which may be the same or different, each signifies methyl or ethyl.

As will be appreciated by one skilled in the art, by virtue of the carbonyl group present in the compounds of formula VI, these compounds may be used to prepare a wide variety of compounds, for example a number of the compounds of formula I, as described in our <sup>patent specification no. 477,574.</sup> ~~pending Application No. 51834/73.~~

The following Example illustrates the invention.

EXAMPLE: 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-  
dibenzo[a,d]cyclohepten-5-one hydrochloride

a) 2-(β-[2-Dimethylaminoethyl]phenethyl)benzoic acid  
hydrochloride (compound of formula X)

5 A solution of 14.75 g (0.05 mole) of 3-(2-  
18,586/76 dimethylaminoethyl)-3,4-dihydro-3-phenylisocoumarin in  
150 ml ethanol containing 1 g 10% palladium on charcoal  
is hydrogenated at 50 psi and room temperature until one  
equivalent of hydrogen is absorbed. The mixture is  
10 filtered and evaporated to give the intermediate 2-[2-  
dimethylaminoethyl]phenethyl) benzoic acid hydrochloride  
form, m.p. 152° to 154°C.

b) 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-dibenzo  
[a,d]cyclohepten-5-one hydrochloride (compound of  
15 formula VI)

A mixture of 14.75 g (0.05 mole) of 2-(β-[2-  
dimethylaminoethyl]phenethyl)benzoic acid hydrochloride  
and 150 g of polyphosphoric acid is heated at 110°C for  
6 hours, allowed to cool and poured on to crushed ice  
20 with stirring. The resulting solution is cooled on ice  
and made basic by the addition of solid potassium  
hydroxide, and extracted with methylene chloride. The  
methylene chloride is washed with water, dried over  
anhydrous magnesium sulfate and evaporated in vacuo.

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The residue is dissolved in isopropanol, and treated with gaseous hydrogen chloride. The resulting precipitate is filtered and recrystallized from isopropanol to give the compound 10-(2-dimethylaminoethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one hydrochloride, m.p. 188-190°C.

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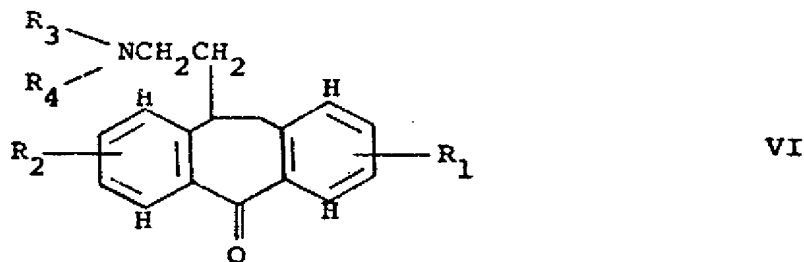
Following the above procedure and using an equivalent amount of ferric chloride in place of polyphosphoric acid, there is obtained the identical product.

Similarly using ferric chloride and 2-( $\beta$ -[2-dimethylaminoethyl]-phenethyl)benzoic acid chloride in place of 2-( $\beta$ -[2-dimethylaminoethyl]phenethyl)benzoic acid hydrochloride, the identical product is again obtained.

Following the above detailed procedure but using 16.3 g of 2-( $\beta$ -[2-dimethylaminoethyl]phenethyl)benzoic acid ethyl ester in place of 14.75 g of 2-( $\beta$ -[2-dimethylaminoethyl]phenethyl)benzoic acid hydrochloride, there is again obtained the identical product.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-  
~~WHATONECCLBTKX19X~~

1. A process for the production of a compound  
of formula VI,

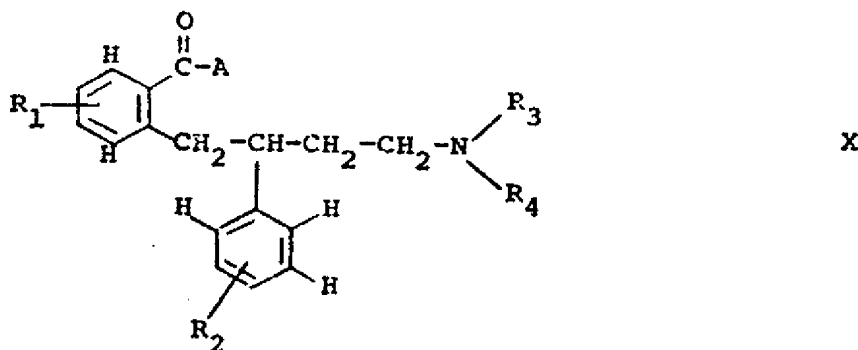


in which R<sub>1</sub> signifies hydrogen, alkyl or  
alkoxy of 1 to 3 carbon atoms or  
fluorine,

R<sub>2</sub> signifies hydrogen, alkyl or  
alkoxy of 1 to 3 carbon atoms,  
fluorine or trifluoromethyl, and

R<sub>3</sub> and R<sub>4</sub> independently signify alkyl  
of 1 to 3 carbon atoms,

comprising cyclising, in the presence of a Lewis acid,  
a compound of formula X,



in which  $R_1$  to  $R_4$  are as defined above, and

A signifies hydroxyl, straight chain alkoxy of 1 to 4 carbon atoms or chlorine.

5                    2. A process according to Claim 1, in which  
the cyclisation is effected in the presence of an inert  
organic solvent.

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10                   3. A process according to Claim 1 or 2, in  
which the reaction is effected at a temperature of  
from 20 to 150°C.

4. A process according to Claim 1, substantially  
as hereinbefore described with reference to the Example.

15                   5. A compound of formula VI, stated in Claim 1,  
whenever produced by a process according to any  
preceding claim.

6. A compound of formula VI, stated in Claim 1.

20                   7. A compound of formula VI, stated in Claim 1,  
in which  $R_1$  and  $R_2$ , which may be the same or different,  
each signifies hydrogen or fluorine, and  $R_3$  and  $R_4$ ,  
which may be the same or different, each signifies  
methyl or ethyl.

8. 10-(2-Dimethylaminoethyl)-10,11-dihydro-5H-  
dibenzo[a,d]cyclohepten-5-one.

DATED            this            11            day of            October            1976.

DAVIES & COLLISON

Patent Attorneys for

SANDOZ PATENTS LIMITED